REMARKS

This amendment is responsive to the non-final Office Action mailed January 13, 2003. Original Claims 1-49 were subject to a restriction requirement resulting in Claims 8-49 being withdrawn from consideration. Claims 1-7 were elected and are under examination in the present action. Claim 1 has been amended to incorporate former dependent Claim 3, which is hereby cancelled. Support for the amendment to Claim 1 is apparent from original Claims 1 and 3. New Claim 50 is added to specifically recite preferred ligand recognition sequences discussed in the application, e.g., at page 17.

Response to issues presented under 35 U.S.C. §112

Claims 1-7 stand rejected under 35 U.S.C. §112, first paragraph, as being deemed to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Particularly, the Examiner states: "It is not seen how applicants arrived at the limitations of the instant claims and for the reasons outlined *supra*, it is maintained that the limitations are not justified or enabled." Applicants traverse.

Applicants first note for the record that the Examiner has misstated the screening process in which Applicants discovered the novel enterokinase cleavable sequences. The Examiner states that "[f]ive rounds of this incubation with enterokinase were performed with increasing stringency and presumably the positive phage from the preceding round was used for the next round." (Office Action, paper no. 11, page 4). This is not entirely accurate, as it is only in rounds 4 and 5 that the stringency of the screening was increased, i.e., by lowering the enterokinase concentration to which the streptavidin-bound, enterokinase susceptible phage were exposed. As explained at pages 33-34 of the application, separate aliquots of phage were treated with 320 nM enterokinase and 1300 nM enterokinase in rounds 1-3; in round 4, the 320 nM phage isolates were treated with 65 nM enterokinase for 30 minutes, then an additional 90 minutes; and in round 5, the 30-minute phage isolates of round 4 were treated with either 10 nM or 30 nM enterokinase. As explained on page 33, the stringency of the isolation rounds was increased in this way to try to force a consensus in enterokinase cleavage sequence pattens in the phage recovered.

The crux of the Examiner's rejection appears to concern the fact that not all of the Round 5 isolates are covered by Claim 1, and, conversely, that some of the embodiments in Claim 1 were not

isolated in Round 5. Additionally, the Examiner notes that the instant claims do not require streptavidin binding sites be present nor do they require a factor Xa cleavage site, "as was the case in the experimental phage displays." (Office Action, paper no. 11, page 4).

Applicants traverse.

First, Applicants note that the enterokinase (EK) susceptible phage isolates of each round were all cleaved by enterokinase. Therefore, each of the sequences disclosed in Tables 1-4 is a functional enterokinase recognition sequence. These individual EK recognition sequences are claimed directly in Claim 13. Round 5 was merely the most stringent screening example.

The Examiner correctly notes that there is no example of threonine (Thr) in the Xaa_4 amino acid position, as recited in Claim 1, among the sequenced isolates in Table 4 (Round 5). Accordingly, the Examiner questions whether Applicants were in possession of the polypeptide claimed at the time of filing. Applicants point out that EK recognition sequences including threonine at the Xaa_4 position are present in several Round 4 isolates, namely, SEQ ID NOs: 67, 72, 89, 128, and 133. (*See* Table 3, pages 36-37). Moreover, once the D-R motif was discovered, Applicants chemically synthesized additional enterokinase cleavage sites containing the D-R↑ motif to further test the rate and extent of cleavage. Of these five additionally synthesized test peptides, three contained the T-D-R↑ motif that the Examiner questions as unsupported/non-enabled. (*See*, e.g., Table 6 and its context on pages 40-41; SEQ ID NOS: 199, 202, and 203). Additionally, of those five synthesized test cleavage sequences, all proved to be EK-cleavable, with test peptide GNY**TDR**↑MFI (SEQ ID NO: 199) showing a cleavage rate over twice as rapid as the known enterokinase recognition sequence GDDDDKIYV (SEQ ID NO: 197). (*See* Tables 6-8 and their accompanying description, pages 40-42).

The particular parameters of the EK cleavable polypeptide recited in Claim 1 are derived from the teaching at the bottom of page 44 of the application, *viz.*:

> "Analysis of the sequence information from screening Rounds 4 and 5 was performed to detect preferences for amino acids at the positions upstream of the scissile bond, in order to select preferred EK cleavage sequences. For the most numerous group, i.e., cleavage sequences having the Asp-Arg motif at the P_2 and P_1 positions, an amino acid was regarded as preferred at a given position in the sequence if it occurred in five or more isolates. Where a phage residue occurred at a given

position, it was not counted. From this analysis, a family of preferred EK recognitions sequences was defined having the following formula:

Xaa_1-Xaa_2-Xaa_3-Xaa_4-Asp-Arg-Xaa_5 (SEQ ID NO:206),

wherein Xaa_1 is an optional amino acid residue which, if present, is Ala, Asp, Glu, Phe, Gly, Ile, Asn, Ser, or Val; Xaa_2 is an optional amino acid residue which, if present, is Ala, Asp, Glu, His, Ile, Leu, Met, Gln, or Ser; Xaa_3 is an optional amino acid residue which, if present, is Asp, Glu, Phe, His, Ile, Met, Asn, Pro, Val, or Trp; Xaa_4 is Ala, Asp, Glu, or Thr; and Xaa_5 can be any amino acid residue."

Therefore, it is clear that Applicants were not only in possession of the subject matter of the present claims, but were also aware of, and distinctly teach, the novel enterokinase recognition sequences of Claim 1.

The Examiner also notes that Claims 1-7 do not require streptavidin binding sites to be present and do not require a factor Xa cleavage site, "as was the case in the experimental phage displays." (Office Action, paper no. 11, page 4). However, it is not a requirement of 35 U.S.C. §112 that the claims reflect the experimental conditions leading to the discovery of the invention. The object of the invention was to provide novel enterokinase recognition sequences, and these are specifically and clearly defined in the claims. Thus, no issue under 35 U.S.C. §112 is seen to arise from the absence of any particular experimental conditions from the claims.

One who discovers a new product is entitled to claim *the product*; he or she is not limited to, or even required to recite in the claims, *how* the product was discovered. Those details belong in the specification and are required for purposes of teaching one of skill in the art how to make and use the invention; such details do not, however, belong in the claims. As the CAFC has straightforwardly stated, "Specifications teach. Claims claim." *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121, 227 USPQ 577, 585, n.14 (Fed. Cir. 1985).

Notwithstanding the foregoing, Applicants note that pending Claim 1 has been amended herein to incorporate the recitation of original Claim 3, and thus the amended claims specifically recite an enterokinase cleavable polypeptide having a ligand binding site included in the polypeptide. The

Examiner may regard this as relevant to the comment comparing the present claims with the experimental phage display, even though Applicants regard this as presenting no issue under 35 U.S.C. §112.

For the foregoing reasons, removal of the rejections under 35 U.S.C. §112 is believed to be in order.

Response to issues presented under 35 U.S.C. §102 and §103

In the Office Action, Claims 1, 6, and 7 stand rejected under 35 U.S.C. §102(b) as being anticipated by any of Denhez et al. (1994) *J. Biol. Chem.* 269(23):16170-16179 (hereinafter *Denhez*); Escriva et al. (1997) *Proc. Natl. Acad. Sci. USA* 94:6803-6808 (hereinafter *Escriva*); Dear et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:4431-4435 (hereinafter *Dear*); Hollander et al. (1996) *Nucleic Acids Research* 24(9):1589-1593 (hereinafter *Hollander*); Kerfeld et al. (1994) *Biochemistry* 33:2178-2184 (hereinafter *Kerfeld*); and Morris et al. (1995) *J. Bacteriology* 177(23):6825-6831 (hereinafter *Morris*). Similarly, Claims 1 and 3-7 stand rejected under 35 U.S.C. §102(b) as being anticipated by, or, in the alternative, under 35 U.S.C. §103(a) as obvious over, *Denhez*, *Escriva*, *Dear*, *Hollander*, *Kerfeld*, or *Morris*.

A rejection for anticipation under 35 U.S.C. §102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. *See* MPEP §2131. Whereas the references of record fail to disclose or suggest aspects of the invention that are particularly and distinctly claimed, reconsideration and withdrawal of the rejections under 35 U.S.C. §102 are requested.

First and foremost, Applicants note that none of the references cited teach novel EK recognition sequences. They are merely being relied upon as allegedly anticipatory art because they disclose one of the following sequences located somewhere within a larger polypeptide: ADR, DDR, EDR, or TDR. However, none of the references contains any teaching or suggestion that any of the disclosed proteins is recognized at that sequence by enterokinase. In the present case, the Examiner cannot presume that any protein that includes a ADR, DDR, EDR, or TDR motif will be cleaved by enterokinase for the purposes of examining Applicants' claims against the prior art, because only Applicants' own disclosure teaches these sequences as EK recognition sequences. It appears the Examiner contends that some of the EK recognition sequences have been found within non-relevant, larger proteins, and concludes that the fact

that they are cleavable by enterokinase is an inherent property of the sequence. This argument, however, is without merit, as inherency cannot be based on the knowledge of the inventor. Rather, facts asserted to be inherent in the prior art must be shown by evidence from the prior art. (*See, In re Dembiczak*, 175 f.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); criticizing the "hindsight syndrome wherein that which only the inventor taught is used against its teacher.")

Furthermore, a rejection under 35 U.S.C. 102 cannot be based on the probability of inherency. As the CAFC has stated:

> "To serve as anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the *missing descriptive matter is necessarily present* in the thing described in the reference, and ***that it would be so recognized by persons of ordinary skill... Inherency ... may not be established by probabilities or possibilities.*** *The mere fact that a certain thing* ***may*** *result from a given set of circumstances is not sufficient.*" *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991) (citations omitted) (emphasis added).

In the present case, none of the cited art teaches enterokinase recognition sequences. Thus, the question is not whether the cited art inherently contains an EK cleavable sequence, but rather whether one skilled in the art would read the cited references as inherently disclosing enterokinase recognition sequences. (*See, Rosco, Inc. v Mirror Lite Co.*, 304 F.3d 1373, 64 USPQ2d 1676 (Fed. Cir. 2002); holding that a patent was not inherently anticipated because there was no evidence that one skilled in the art would read the allegedly anticipating art as showing a mirror of varying radius of curvature along the major axis.) Similar to the situation in *Rosco*, the present Examiner points to no evidence that one skilled in the art would read the cited references as teaching, or even disclosing, EK recognition sequences. Instead, the Examiner inappropriately relies on the *teachings of the Applicant's own specification*, not the knowledge of one skilled in the art, to show that the subject amino acid sequences have the ability to act as enterokinase recognition sequences. Furthermore, the Examiner rejects the present claims as anticipated based on the *probability* that enterokinase can *access* the recognition sequences, taught by Applicants disclosure, located with a large protein structure. The law allows neither of these assumptions. As stated above, a rejection based on inherency requires that the missing descriptive material is necessarily present, and that it would be so recognized by persons or ordinary skill in the art.

For the foregoing reasons, the invention as claimed in Claim 1, namely, a polypeptide comprising an enterokinase recognition sequence *and* having a specified amino acid structure, is not found in any of the prior art references of record. Hence, none of the cited references can anticipate Claim 1 or claims depending therefrom as a matter of law.

Notwithstanding the foregoing, however, Applicants wish to point out that amended Claim 1 now specifically recites and additional feature, "wherein Z_1 is a ligand recognition sequence" incorporated from original Claim 3. None of the prior art cited teach or disclose a polypeptide comprising an EK recognition sequence of the present invention and further containing a ligand recognition sequence adjacent said EK recognition sequence. Thus, none of *Denhez*, *Escriva*, *Dear*, *Hollander*, *Kerfeld*, or *Morris* anticipate, or renders obvious, any of the present claims as amended.

In view of the amendments to the claims herein and the foregoing remarks, reconsideration and withdrawal of the rejections of Claims 1 and 3-7 under 35 U.S.C. §102(b) and/or 35 U.S.C. §103(a) are respectfully requested.

Every effort has been made to advance the case to allowance, to particularly and distinctly define the subject matter of the invention, and to distinguish the invention over the prior art of record. In view of the amendments herein and the foregoing remarks, reconsideration and allowance of the claims as amended are respectfully requested. The Examiner is requested to contact the undersigned by telephone if any further issues are deemed to remain.

Respectfully submitted,

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Appendix A

COMPLETE CLAIMS IN Ser. No. 09/884,767
(marked set showing deletions ~~by strikethrough~~ and additions by underlining)

1. **(Currently amended)** A polypeptide comprising an enterokinase recognition sequence and having the formula:

(1) Z_1-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Asp-Arg-Xaa_5-Z_2 (SEQ ID NO:1),

wherein Xaa_1 is an optional amino acid residue which, if present, is Ala, Asp, Glu, Phe, Gly, Ile, Asn, Ser, or Val; Xaa_2 is an optional amino acid residue which, if present, is Ala, Asp, Glu, His, Ile, Leu, Met, Gln, or Ser; Xaa_3 is an optional amino acid residue which, if present, is Asp, Glu, Phe, His, Ile, Met, Asn, Pro, Val, or Trp; Xaa_4 is Ala, Asp, Glu, or Thr; and Xaa_5 can be any amino acid residue; and wherein Z_1 is a ligand recognition sequence, and Z_2 ~~are both optional and are, independently, polypeptides~~ is an optional polypeptide of one or more amino acids.

2. **(Original)** The polypeptide of Claim 1, wherein Xaa_1 is Asp, Xaa_2 is Ile, Xaa_3 is Asn, Xaa_4 is Asp, and Xaa_5 is Met, Thr, Ser, Ala, Asp, Leu, Phe, Asn, Trp, Ile, Gln, Glu, His, Val, Gly, or Tyr.

3. **(Cancelled)** ~~The polypeptide of Claim 1, wherein Z_1 is a ligand recognition sequence.~~

4. **(Original)** The polypeptide of Claim 1, wherein Z_1 is a streptavidin binding domain.

5. **(Original)** The polypeptide of Claim 4, wherein the streptavidin binding domain is selected from the sequences: His-Pro-Gln-Phe (SEQ ID NO:6), Cys-His-Pro-Gln-Phe-Cys (SEQ ID NO:5), Cys-His-Pro-Gln-Phe-Cys-Ser-Trp-Arg (SEQ ID NO:7), Trp-His-Pro-Gln-Phe-Ser-Ser (SEQ ID NO:210), Pro-Cys-His-Pro-Gln-Phe-Pro-Arg-Cys-Tyr (SEQ ID NO:211), and tandemly arranged combinations and repeats thereof.

6. **(Original)** The polypeptide of Claim 1, wherein Z_2 is a protein of interest.

7. **(Original)** The polypeptide of Claim 1, wherein the polypeptide Xaa_5-Z_2 is a protein of interest.